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<p>(54) Title: TRANSDERMAL DELIVERY OF MEDICATIONS USING A COMBINATION OF PENETRATION ENHancers</p> <p>(57) Abstract</p> <p>A composition and procedures for its formation and administration are described, which provide for a convenient, efficacious and simple transdermal administration of medications from a topically applied cream. No transmission through a membrane is involved. The composition incorporates at least two separate penetration enhancers which function synergistically to provide for rapid but controllable transport of the medication from the cream into the skin. The use of a plurality of penetration enhancers, at least one of which facilitates the separation of medication from the cream and at least a second of which alters the structure of the outer layers of skin, particularly the stratum corneum, enhances migration of the drug through the stratum corneum.</p>			
<pre>     graph TD       subgraph Top         A[FORMATION OF ORGANOGL] --&gt; B[MIX]         B --&gt; C[SOLUBILIZATION OF DRUG]         C --&gt; D[MIX]       end       subgraph Bottom         E[FORMATION OF CARRIER AND DRUG RELEASE AGENT] --&gt; F[MIX]         F --&gt; G[PH ADJUSTMENT IF NECESSARY]         G --&gt; H[FINISHED PRODUCT]       end       D --&gt; E       D --&gt; F       LECITHIN --&gt; A       ISOPROPYL PALMITATE --&gt; A       DRUG --&gt; C       SOLVENT --&gt; C       POLYOXYMER --&gt; E       WATER --&gt; E   </pre>			

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**TRANSDERMAL DELIVERY OF MEDICATIONS USING  
A COMBINATION OF PENETRATION ENHANCERS**

**BACKGROUND OF THE INVENTION**

5      *Field of the Invention:*

The invention herein relates to the transdermal delivery of medications to a patient. More particularly it relates to compositions which allow medication molecules to be solubilized and delivered transdermally and to methods for formation of such compositions and for their therapeutic use.

10     (For convenience herein the terms "drug" and "medication" may be used interchangeably. We wish to emphasize, however, that this invention is applicable to the delivery of any type of compound or molecular species which is intended to be administered to a patient transdermally for a therapeutic or physiological purpose. Whether the material happens to meet a particular 15 specific definition of a "drug" or "medication" or other applicable term is not critical for the purposes of this invention, and the invention should not be limited by the particular term applied to the material being administered.)

*Description of the Prior Art:*

In the past the delivery of medications transdermally to a patient has been 20 limited to administration by transcutaneous injection or by transdermal migration from a patch placed on the outer surface of the patient's skin. The deficiencies of administration by injection are obvious. With only a few exceptions injections must be administered by trained and qualified medical personnel. The injection itself causes a break in the skin which can lead to infection, despite precautions; 25 an injection needle may itself be contaminated causing infection to the patient; and, course, it is a simple fact that injections are uncomfortable to almost all patients. Further, an injection is normally not "location specific." Rather the injection is made at a location on the body remote from the affected area, and the injected medication must be transported through the body to that location.

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This results in losses in transport, so that to administer an effective amount of medication to the affected area, and excess of medication must be injected.

In view of these deficiencies of injection administration, significant effort has been spent in the last few years in seeking alternative methods of transdermal administration of medications. It has been necessary to meet two requirements. First, the method must provide for extended containment of the drug and any carrier while in place on the patient's skin (in effect analogous to containment of the medication and carrier in the reservoir vial of the injection syringe), in a form that does not lend itself either to contamination of the medication and carrier or to loss of the medication and carrier. Second, the systems employed must provide for a regulated and predictable rate of transfer of the medication (with or without the carrier) from the containment device into and through at least some layers of skin to where the medication will be dispersed throughout the affected area of the body.

The only workable prior art embodiment of such a device has been what is commonly known as a "patch." A patch is generally a flat hollow device with a permeable membrane on one side and also some form of adhesive to maintain the patch in place on the patient's skin, with the membrane in contact with the skin so that the medication can permeate out of the patch reservoir and into and through the skin. The outer side the patch is formed of an impermeable layer of material, and the membrane side and the outer side are joined around the perimeter of the patch, forming a reservoir for the medication and carrier between the two layers.

Numerous kinds of medications have been administered through the use of a patch, notably scopolamine for preventing motion sickness, nicotine derivatives intended to discourage an addicted smoker from continuing the smoking habit and estrogen hormones.

Patches have their own set of disadvantages. A principal disadvantage is that, notwithstanding the presence of a penetration enhancer, the delivery of

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the medication is necessarily limited by the rate of passage of the medication through the patch membrane to the skin. Since the medication is not in contact with the skin while it is enclosed in the patch, whatever length of time is required for the medication to permeate through the skin itself to become effective is  
5 necessarily lengthened by the time needed for the medication first to exit from the patch through the membrane. In many cases the membrane permeation rate is the significant rate limiting step of speed of effectiveness of a particular medication, and can render patch administration essentially ineffective because the medication cannot reach the patient's system rapidly enough to be  
10 efficacious. In addition, the adhesive which is intended to secure the patch to the patient's skin can fail, so that the patch disengages from the skin before completion of the transfer of the medication, resulting in loss of that quantity of medication which remains within the patch's reservoir.

Various methods have been used to increase skin permeation of  
15 medications, including penetration enhancers, pro drugs, superfluous vehicles, iontophoresis, phonophoresis and thermophoresis. For the purposes of this invention, only the penetration enhancers are relevant. Ideal enhancers have no irritancy and toxicity to the skin, and the whole body, together with having high enhancing effects. Enhancers themselves should be physiochemically  
20 stable and not have pharmacologic effects, and preferably should not have smell, color, or taste. A typical example of an enhancer is disclosed in U.S. Patent No. 4,783,450 (to Fawzi et al.) in which lecithin is used for penetration enhancement.

The stratum corneum provides the principal barrier to the percutaneous  
25 penetration of topically applied substances. It is the most superficial cutaneous layer and is a horny layer that consists of flat, scalelike "squames" made up of the fibrous protein keratin. The squames are continually being replaced from below by epidermal cells that die in the process of manufacturing keratin. It is unlikely that the emulsified fat on the skin surface greatly affects permeability.

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However, vehicles can control, to a great extent, the rate of penetration of drugs that are applied to the skin. The intercellular lipids may be important for the permeability barrier in skin.

It is known that some combinations of enhancers and vehicles act synergistically, such as the combination of ethanol as a vehicle for the enhancer laurocapram. However, many combinations are not synergistic; for instance, n-decylmethylsulfoxide lowers the zeta potential of the skin, and thus enhancement due to conduction flow (iontophoresis) is minimized. In the past, synergism of combinations could not be predicted.

Further, one must differentiate between penetration enhancer which act to improve the ability of the medication to pass through a patch membrane to reach the skin, and those which act to enhance the separation of the medication from its carrier matrix or to enhance the diffusion of the medication into and through the skin.

However, notwithstanding the various deficiencies mentioned, administration by injection or by patch remain only by viable transdermal administration techniques known to the prior art.

#### SUMMARY OF THE INVENTION

We have now developed a system that provides for a convenient, efficacious and simple system for transdermal administration of medications in which the medication is present in a composition for direct application to the skin, commonly in the form of a cream or similar material. The transdermal administration of the drug is therefore not hindered by having to penetrate a patch membrane, since the cream and its medication content are directly in contact with the skin and the medication needs only to separate from the cream in order to be available for transdermal migration. In addition, since the composition is in the form of a cream or other viscous moldable and spreadable material, the drug may be effectively administered by application of the cream

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to many bodily areas where a patch either will not fit or cannot be shaped to conform to the skin contours.

(As with the use of the terms "medication" and "drug," our invention is not to be limited by the term used to describe the physical properties of the composition herein. We will for convenience use the term "cream," but other terms such as "gel," "lotion," "paste" and the like also could be applicable. As will be seen from the description below, the physical nature of the composition containing the medication and to be applied to the patient's skin will be defined by functional parameters, rather than being limited by an arbitrary descriptive term.)

A key element in the success of the present invention is our discovery that the use of at least two separate penetration enhancers of defined function results in a synergism which provides rapid but controllable separation of the medication from the cream and its penetration into and within or through the skin. At least one of the penetration enhancers acts to facilitate the separation of drug from the carrier within the cream and at least a second penetration enhancer alters the structure of the outer layers of skin, particularly the stratum corneum, such that migration of the drug through the stratum corneum is enhanced and expedited. The medication is thus taken up by the patient's system and is efficacious much more rapidly than would be the case for administration of the medication by means of the prior art patch system. Further, although permeation of the skin does not provide for as rapid administration by the medication as would result from direct injection, the use of the present invention avoids the problems associated with injection administration.

Therefore, in one principal embodiment, the invention is of a composition for diffusional transdermal delivery of medication to a patient, which comprises a medication capable of being administered transdermally; a carrier for the medication; a first penetration enhancer which improves diffusion of the medication into and within the patient's skin; and a second penetration enhancer

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which improves diffusion of the medication out of the composition for transdermal migration; the composition having a viscosity in a range such that it may be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered  
5 transdermally to the patient.

In another principal embodiment, the invention is of a method for the preparation of a therapeutic composition to be transdermally administered which comprises solubilizing a medication capable of being administered transdermally; forming an organogel comprising a first penetration enhancer which improves  
10 diffusion of the medication into and within the patient's skin, and a carrier for the solubilized medication; forming a polymeric component comprising a second penetration enhancer which improves diffusion of the medication out of the composition for transdermal migration; and blending the solubilized medication, organogel and polymeric component to form the composition having a viscosity  
15 in a range such that it may be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered transdermally to the patient.

In yet another principal embodiment, the invention is of a method for the transdermal administration of a medication which comprises solubilizing a  
20 medication capable of being administered transdermally; forming an organogel comprising a first penetration enhancer which improves diffusion of the medication into and within the patient's skin, and a carrier for the solubilized medication; forming a polymeric component comprising a second penetration enhancer which improves diffusion of the medication out of the composition for  
25 transdermal migration; blending the solubilized medication, organogel and polymeric component to form the composition having a viscosity in a range such that it may be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered transdermally to the patient; and applying the composition to the skin

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of a patient for the period of time and allowing the medication to diffuse out of the composition and through the skin, such that the medication is taken up by the body of the patient and acts therapeutically on the patient.

In preferred embodiments the first penetration enhancer is a lecithin organogel formed with isopropyl palmitate or isopropyl myristate, and the second penetration enhancer is a polyoxymer, preferably a polyoxyalkylene derivative of propylene glycol. A wide variety of medications can be delivered by this invention. Further, while the invention herein is described in terms of the minimum number of synergistically acting penetration enhancers (i.e., two), it will be understood that additional penetration enhancers can also be present. Thus there may be more than one enhancer which operates with a specific mechanism, or there may be additional enhancers which provide yet other modes of operation, or both.

The methods and compositions described herein provide a unique and highly effective technique for administering medication directly to an affected area of the body with the minimum amount of medication and with the avoidance of unwanted side effects. Unlike administration by injection or orally, the transdermal administration herein is site specific; the cream is applied to the skin directly at the affected area of the body. There are therefore no losses of medication during transport from a remote application site. Similarly, the long delays in having an effective quantity of the medication reach the affected area of the body, which are inherent in injection and oral administration, are entirely eliminated in the present invention.

The present method also avoids unwanted side effects. For instance, in oral administration of a medication, the medication itself can adversely affect the gastrointestinal tract as it is swallowed and dissolved for assimilation into the circulatory system. Those skilled in the art are well familiar with the common caution required for many oral medications that they must be administered only in conjunction with a meal, or, conversely, that they cannot be administered in

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the presence of specific types of food products, such as dairy products. These cautions are necessary since the orally administered medication's efficacy will be adversely affected by certain foods, or the person's gastrointestinal tract will be irritated by the medication if the latter is not diluted by the presence of food  
5 in the gastrointestinal tract. Such considerations are, of course, entirely absent in the present invention, where the same medications can be easily and conveniently administered transdermally without incurring such side effects.

Further, the transdermal administration avoids the "first pass effect," which often results when a medication is administered orally and thus has to  
10 pass through various organs, including the liver, before reaching the affected area of the body. These organs can absorb or chemically alter significant quantities of the passing medication, thus requiring that large excess quantities of the medication be administered initially to insure that an effective quantity of the medication will ultimately reach the affected area of the body. Since in this  
15 method the medication commonly passes through the skin directly to the affected site, there is no problem of loss in intermediate organs, and therefore excessive quantities of medication do not need to be delivered to counter such losses. (As an example, ketoprofen is commonly administered orally in quantities of about 50-75 mg per dose for the desired efficacy. In the present  
20 invention, however, an equally effective dose of ketoprofen can be delivered by topical transdermal administration of only 3 mg.)

Finally, since the present invention is site specific, the depth of delivery of the medication can be readily controlled, as contrasted to injection delivery.

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#### BRIEF SUMMARY OF THE DRAWING

The single Figure of the drawing is a flow chart illustrating schematically formulation of a preferred embodiment of a composition of this invention.

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### DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

The unique compositions of the present invention require a specific sequence of steps in their formation if a therapeutically effective and pharmaceutically compatible composition is to be obtained. This is best  
5 understood by reference to the Figure of the drawing.

The basic composition of this invention is a mixture of an organogel, a solubilized medication or drug and a carrier combined with a drug release agent. Penetration enhancement is provided by the organogel and by the release agent.

10 In the exemplary process as illustrated in the Figure, an organogel is formed, in this example from lecithin and isopropyl palmitate. These two materials are thoroughly blended and mixed until a substantially uniform gel structure forms. The organogel, which is the base for the cream composition, should be formed at the time that the composition is to be formulated. The drug  
15 or medication is solubilized with a solvent, such as water, alcohol or other appropriate solvent, again by mixing in a known manner. When it is desired to start formation of the actual composition, the solubilized drug is mixed thoroughly into the organogel matrix, again by conventional mixing techniques. The technique used will of course be such that the organogel's structure is not  
20 broken down. Finally, a carrier, such as water or alcohol, and a drug release agent, such as a polyoxymer, are blended. The carrier/release agent mixture can be made up in large lots and stored under refrigerator until needed, at which  
time an appropriate quantity can be taken for and the remainder retained in  
refrigerated storage. The carrier/release agent mixture is then mixed with the  
25 drug/organogel mixture to produce the final "cream" composition. Details will be provided below.

Considering first the organogel, the blend of the two components will be in the range of from about 25% to 75% of the lecithin component, the remainder being the fatty acid ester component. (Unless stated otherwise, all percentages,

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parts and concentrations are by weight.) The "lecithin component" may be lecithin, any comparable fatty acid phospholipid emulsifying agent, such as fatty acids and their esters, cholesterol, tri-glycerides, gelatin, acacia, soybean oil, rapeseed oil, cottonseed oil, waxes or egg yolk, or any other material which acts

5 in the same manner as lecithin.

The other component is an organic solvent/emollient, particularly including fatty acid esters, of which the esters of the saturated alkyl acids are preferred.

The preferred solvent/emollient in the present invention is isopropyl palmitate or isopropyl myristate. However, there are numerous compounds available which

10 exist in liquid form at ambient temperatures and will function in a manner equivalent to the fatty acid esters. These are all quite well known and described.

They include, but are not limited to, the following:

	Ethanol	Laurocapram (azone)
	Propylene glycol	(1;1-dodecylazacycloheptan-2-one)
15	Water	Acetonitrile
	Sodium oleate	1-decanol
	Leucinic acid	2-pyrrolidone
	Oleic acid	N-methylpyrrolidone
	Capric acid	N-ethyl-1-pyrrolidone
20	Sodium caprate	1-methyl-2-pyrrolidone
	Lauric acid	1-lauryl-2-pyrrolidone
	Sodium laurate	Sucrose monooleate
	Neodecanoic acid	Dimethylsulfoxide
	Dodecylamine	Decylmethylsulfoxide
25	Cetyl lactate	Acetone
	Myristyl lactate	Polyethylene glycol (100-400mw)
	Lauryl lactate	Dimethylacetamide
	Methyl laurate	Dimethylformamide
	Phenyl ethanol	Dimethylisosorbide
30	Hexamethylene lauramide	Sodium bicarbonate
	Urea and derivatives	Various C <sub>7</sub> to C <sub>16</sub> alkanes
	Dodecyl n,n-dimethylamino acetate	Mentane
	Hydroxyethyl lactamide	Menthone
	Phyophatidylcholine	Menthol
35	Sefsol-318 (a medium chain glyceride)	Terpinene
	Isopropyl myristate	D-terpinene
	Isopropyl palmitate	Dipentene
	Surfactants (including):	N-nonalol
	polyoxyethylene (10) lauryl ether	Limonene
40	diethyleneglycol lauryl ether	Ethoxy diglycol

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This combination of the phospholipid emulsifying agent and the fatty acid or fatty acid ester or equivalent thereof forms an organogel. In the example referred to in the Figure, the organogel will be a lecithin organogel, which is both isotropic and thermally reversible. At temperatures greater than about 40°C the 5 organogel will become a liquid and its viscosity will be greatly reduced. Water can be also be added to control the viscosity of the organogel. The organogel serves as one of the penetration enhancers in the cream, and acts on the stratum corneum of the skin to promote interaction between the phospholipids of the cream and the phospholipids of the skin. This causes a disruption in the 10 normal regular arrangement of layers in lipids in the stratum corneum so that openings are created which then allow the drug to pass more easily through the skin. The organogel will be compatible with a wide variety of lipophilic, hydrophilic and amphoteric drugs and medications.

Using the above-described lecithin organogel and its components as an 15 example, the properties needed for inclusion of a components in this invention will be evident. The various compounds, polymers, etc. comprising the organogel, the solubilized drug and the carrier/polyoxymer components must all be compatible with each other, so that chemical reactions do not occur which would adversely affect the efficacy or safety of the cream composition; they must 20 be mutually soluble so that they can be mixed and blended to a uniform consistency; they must be such that the resulting cream composition has a viscosity under ambient conditions which is low enough to allow it to be applied easily and smoothly to the skin, but not so low that the cream acts as at least in part like a liquid and cannot be retained on the skin where it is applied; they must 25 not be toxic, irritating or otherwise harmful to the patient; they must be sufficiently stable that the overall composition will have a reasonable shelf life and service life; and, as a practical matter, they must be available at reasonable cost. Thus, it will generally be found that the characteristics of a drug or medication which make it difficult to administer transdermally through the present

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system include its having low stability, particularly at ambient temperatures; not being soluble in the composition; having high molecular weight resulting in difficulty penetrating the stratum corneum, even with the enhanced openings; and/or causing an adverse reaction with the one or more skin layers.

5       The drug or medication which is to be administered usually must be solubilized in a solvent to enable it be blended properly with the organogel and the carrier/release agent. Typical solvents for such use include water, the low molecular weight alcohols and other low molecular weight organic solvents. Solvents such as water, methanol, ethanol and the like are preferred. The  
10      purpose of solubilizing is to enable the medication to become properly dispersed in the final cream. It is possible that a few drugs or medications might themselves be sufficiently soluble in the cream that a solvent, and therefore a separate solubilizing step, would not be needed. For the purpose of this description, therefore, the term "solubilized" drug or medication shall be  
15      considered to include those drugs or medications which can be dispersed or dissolved into the cream with or without the presence of a separate solvent. Usually the amount each of medication and solvent which will be present, based on the entire composition, will be in the range of up to <1%-20%, with the preferred concentration of each being about 10%. The concentrations of both  
20      need not be identical.

A wide variety of drugs may be transported by this method and through this type of composition. Typical of the various drugs which can be successfully incorporated into the present composition and transdermally transported include the following classes of substances:

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	Antidiabetic Agents	Multivitamin Preparations
	Sulfonylureas	Vitamin Combinations
5	Acetohexamide Chlorpropamide Tolazamide Tolbutamide Glipizide Glyburide Glimepiride Metformin Acarbose Insulin	Antihyperlipidemic Agents
10		Fluvastatin Lovastatin Pravastatin Simvastatin Probucol Niacin Dexothyroxine Clofibrate Gemfibrozil
15	Glucose Elevating Agents	Cardiac Drugs
	Diazoxide Glucose	Cardiac Glycosides
		Digitoxin Digoxin
20	Thyroid Hormones	Antiangular Agents
	Levothyroxine Liothyronine Thyroid USP Thyroglobulin Liotrix	Nitroglycerin Isosorbide Dinitrate Isosorbide Mononitrate
25	Thyroid Drugs	Antiarrhythmic Agents
	Iodine Propylthiouracil Methimazole	Moricizine Quinidine Procainamide Disopyramide Lidocaine Tocainide Mexiletine Flecainide Encainide Amiodarone
30	Parathyroid Drugs	Respiratory Drugs
	Calcitonin Etidronate Pamidronate Alendronate Gallium Nitrate	Bronchodilators
35		Albuterol Metaproterenol Terbutaline Isoproterenol Ephedrine Theophylline Dyphylline
	Vitamins	
40	Vitamin A Vitamin D Vitamin E Vitamin B1 Vitamin B2 Vitamin B3 Vitamin B6 Vitamin B12 Vitamin C (con't. next column)	
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	Nasal Decongestants	Antirheumatic Agents
	Phenylpropanolamine	Gold Compounds
	Pseudoephedrine	Penicillamine
	Phenylephrine	Azathioprine
5	Ephedrine	Methotrexate
	Naphazoline	
	Oxymetazoline	Agents for Gout
	Tetrahydrozoline	Probenecid
10	Xylometazoline	Sulfinpyrazone
	Propylhexedrine	Allopurinol
	Gastrointestinals	Colchicine
	Sucralafate	Agents for Migraine
	Metoclopramide	Sumatriptan
15	Cisapride	Methysergide
	Laxatives	Ergotamine Derivatives
	Mesalamine	
	Olsalazine	Sedatives and Hypnotics
	Antidiarrheals	Zolpidem
20	Famotidine	Paraldehyde
	Nizatidine	Chloral Hydrate
	Cimetidine	Acetylcarbromal
	Rantidine	Glutethimide
	Omeprazol	Ethchlorvynol
25	Cifapride	Ethimetae
	Miscellaneous	Temazepam
	Finasteride	Estazolam
	Lamsoprazole	Flurazepam
30	Papaverine	Quazepam
	Prostaglandins	Triazolam
	Amphetamines	Phenobarbital
	Dextroamphetamine	Mephobarbital
35	Anorexiants	Amobarbital
	Phentermine	Butabarbital
	Benzphetamine	Secobarbital
	Phendimetrazine	Pentobarbital
40	Diethylpropion	
	Mazindol	Antianxiety Agents
	Fenfluramine	Meprobamate
	Dexfenfluramine	Alprazolam
45		Chlordiazepoxide
		Clonazepam
		Clorazepate
		Diazepam
		Halazepam
		Lorazepam
		Oxazepam (con't. next page)

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	Prazepam	Antipsychotic Agents
	Buspirone	Chlorpromazine
	Hydroxyzine	Promazine
5	Doxepin	Trifluopromazine
	Chlormezanone	Thioridazine
	Anticonvulsants	Mesoridazine
	Phenytoin	Acetophenazine
	Mephénytoïn	Perphenazine
10	Ethotoin	Fluphenazine
	Ethosuximide	Trifluoperazine
	Methsuximide	Chlorprothixene
	Phensuximide	Thiothixene
	Paramethadione	Haloperidol
15	Trimethadione	Molindone
	Clonazepam	Loxapine
	Clorazepate	Clozapine
	Valproic Acid	Riperidone
	Lamotrigine	Pimozide
20	Primidone	Prochlorperazine
	Gabapentin	Other Psychotherapeutic Agents
	Phenacemide	Lithium
	Carbamazepine	Methylphenidate
	Phenobarbital	Tacrine
25	Antidepressants	Pemoline
	Amitriptyline	Antimicrobials
	Clomipramine	Antibacterials
	Doxepin	Penicillins
30	Imipramine	Cephalosporins
	Trimipramine	Carbapenems
	Amoxapine	Monobactams
	Desipramine	Chloramphenicoï
	Nortriptyline	Fluoroquinolones
35	Protriptyline	Tetracyclines
	Venlafaxine	Macrolides
	Maprotiline	Spectinomycin
	Trazodone	Vancomycin
	Bupropion	Lincosamides
40	Fluoxetine	Aminoglycosides
	Paroxetine	Colistin
	Sertraline	Polymixin B
	Fluvoxamine	Bacitracin
	Tranylcypromine	Novobiocin
45	Phenelzine	Metronidazole
	Nefazodone	

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	Antifungals	Amantadine Foscarnet Didanosine Acyclovir Ganciclovir Zalcitabine Rimantadine
5	Flucytosine Nystatin Miconazole Ketoconazole Amphotericin B Griseofulvin Fluconazole Itraconazole	
10	Sulfonamides	Miscellaneous Anti-infectives Trimethoprim Trimethoprim-Sulfamethoxazole Erythromycin-Sulfisoxazole Furazolidone Pentamidine Eflofornithine Atovaquone Trimetrexate Glucuronate
15	Sulfadiazine Sulfacytine Sulfamethoxazole Suflamethiazole	
20	Antimalarials	Leprostatics Dapsone Clofazime
	Quinine Sulfate Mefloquine Quinacrine Doxycycline 4-Aminoquinolone Compounds	Antihelmintics Mebendazole Diethylcarbamazine Citrate
25	8-Aminoquinolone Compounds	Pyrantel Thiabendazole Piperazine Quinacrine Niclosamide Oxamniquine
	Folic Acid Antagonists	Praziquantel
30	Antituberculous Drugs	
	Isoniazid Rifampin Rifabutin Ethambutol HCl Pyrazinamide Aminosalicylate Sodium Ethionamide Cycloserine Streptomycin Sulfate Capreomycin	Diphenhydramine Chlorpheniramine Pyrilamine Doxepin Carbinoxamine Clemastine Tripeleannamine Brompheniramine Dexchlorpheniranune Triprolidine Methdilazine Promethazine Trimeprazine (con't. next page)
35	Amebicides	
	Paromomycin Iodoquinol Metronidazole Emetine Chloroquine	
40	Antivirals	
	Famciclovir Stavudine Zidovudine Ribavarin (con't. next column)	

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	Hydroxyzine HCl	Desoximetasone
	Azatadine	Fluocinolone
	Cyproheptadine	Halcinonide
	Phenindamine	Clocortolone
5	Astemizole	Flurandrenolide
	Loratadine	Fluticasone
	Terfenadine	Mometasone
	Cetirizine	Aclometasone
10	Antimetabolites	Desonide
	5-Fluorouracil	Fludrocortisone
	6-Mercaptopurine	Local Anesthetics
	Mycophenolic Acid	Dibucaine
	Methotrexate	Lidocaine
15	Cytarabine	Benzocaine
	Floxuridine	Butamben Picrate
	Thioguanine	Tetracaine
	Anticholinergics	Dyclonine
20	Atropine	Pramoxine
	Scopolamine	Prilocaine
	Homatropine	Antiplatelet Drugs
	Tropicamide	Dipyridamole
	Pirenzepine	Ticlopidine
25	Isopropamide	Warfarin
	Propantheline	Coumarin
	Methscopolamine	Non-steroidal Antiinflammatory Agents
	Methantheline	Fenoprofen
	Trihexyphenidyl	Ibuprofen
30	Benztropine	Flurbiprofen
	Biperiden	Ketoprofen
	Steroidal Antiinflammatory Agents	Naproxen
	Cortisone	Oxaprozin
35	Hydrocortisone	Diclofenac
	Hydrocortisone Acetate	Etdonalac
	Prednisone	Indomethacin
	Prednisolone	Ketorolac
	Triamcinolone	Nabumetone
40	Methylprednisolone	Sulindac
	Dexamethasone	Tolmentin
	Betamethasone	Meclofenamate
	Clobetasol	Flufenamic Acid
	Diflorasone	Mefenamic Acid
	Halobetasol	Meclofenamic Acid
45	Amicinonide (con't. next column)	Piroxicam
		Salicylates (con't. next page)

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	Diflunisal	Carteolol
	Indomethacin	Nadolol
	Phenylbutazone	Penbutolol
	Oxyphenbutazone	Pindolol
5	Sulfinpyrazone	Sotalol
	Allopurinol	Timolol
	Penicillamine	Labetalol
	Colchicine	Ace Inhibitors
	Probenicid	Benazepril
10	Sunscreen Agents	Captopril
	Oxybenzone	Enalapril
	Dioxybenzone	Fosinopril
	p-Aminobenzoic Acid	Lisinopril
15	Ethyl Dihydroxy Propyl PABA	Moexipril
	Padimate O	Quinapril
	Glyceryl PABA	Ramipril
	Cinoxate	Calcium Channel Blockers
	Ethylhexyl p-methoxycinnamate	Diltiazem
20	Octocrylene	Verapamil
	Octyl Methoxycinnamate	Nifedipine
	Ethylhexyl salicylate	Felodipine
	Homosalate	Nicardipine
25	Octyl Salicylate	Nimodipine
	Menthyl Anthranilate	Nisoldipine
	Digalloyl Trioleate	Isradipine
	Avobenzone	Bepridil
	Muscle Relaxants	Amlodipine
30	Carisoprodol	Nisoldipine
	Chlorphenesin	Alpha Blockers
	Chlorzoxazone	Methyldopa
	Cyclobenzaprine	Clonidine
	Metaxalone	Phentolamine
35	Methocarbamol	Guanabenz
	Orphenadrine	Phenoxybenzamine
	Diazepam	Guanfacine
	Baclofen	Yohimbine
40	Antihypertensives	Reserpine
	Beta-Blockers	Guanethidine
	Propranolol	Guandrel
	Acebutolol	Doxazosin
	Betaxolol	Prazosin
45	Bisoprolol	Terazosin
	Esmolol (con't. next column)	Vasodilators
		Hydralazine
		Minoxidil
		Nitroglycerin (con't. next page)

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	Isosorbide Dinitrate Isosorbide Mononitrate Papaverine	Oxymorphone Oxycodone Meperidine Methadone Propoxyphene Tramadol Acetaminophen Pentazocine Fentanyl Salicylates
5	Diuretics  Thiazides Loop Diuretics Spironolactone Triamterene	
10	Acetazolamide Methazolamide Dichlorphenamide	Sex Hormones  Estogens Estriol Estradiol Estrone Testosterone Methyltestosterone Progesterone Medroxyprogesterone Hydroxyprogesterone Norethindrone Megesterol
15	Antiemetics  Chlorpromazine Trifluopromazine Perphenazine Prochlorperazine Promethazine Thiethylperazine Metoclopramide Cyclizine Meclizine Buclizine	
20		Pituitary Hormones DDAVP Methylergonovine
25	Dimenhydrinate Trimethobenzamide Scopolamine Diphenidol Benzquinamide Hydroxyzine	Uterine Hormones Carboprost Dinoprostone
30		Adrenal Steroid Inhibitors Aminoglutethimide
35	Analgesics  Codeine Hydrocodone Hydromorphone Morphine (con't. next column)	In one preferred embodiment, the drug is ketoprofen.

Finally, the carrier and drug release agent form a polymeric composition which provides the separate penetration enhancement of facilitating the rapid release of the medication from the cream upon topical application to the patient. The purpose of this combination of materials is to provide for penetration enhancement of a different type than that of the organogel, i.e., by effecting

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rapid release of the drug from the cream and transport by the carrier out of the cream and into the skin through the enhanced openings in the stratum corneum.

The drug release agent may be any of a variety of polyoxymers, i.e., polyoxyalkylene derivatives of propylene glycol. Preferred are those which  
5 contain mixtures of polyoxyethylene and polyoxypropylene polymeric derivatives of propylene glycol or methyl oxirane polymers. By acting essentially as an emulsifier, stabilizer and dispersing agent, the polyoxymer facilitates the separation of the drug or medication from the other components of the cream and transfers it to the carrier, which will normally be water or a low molecular  
10 weight alcohol or organic solvent. Useful polyoxymers are available under the trademark "Pluronic" from Wyandotte Chemical Company.

The concentration of the carrier provided with the drug release agent as a mixture in the cream will determine the particular diffusion coefficient of the drug. With higher concentrations of the carrier, the diffusion coefficient will be  
15 lower and the drug will be absorbed more slowly and produce more local effects. Conversely, lowering the concentration of the carrier will speed the absorption of the drug and enhance the ability of the drug to be absorbed systemically. The normal concentration of the drug release agent in the mixture with the cream will be approximately 20% to 30%, with the balance being the carrier, during the  
20 formation of the carrier/drug release agent mixture.

The overall concentrations of the various components in the composition will generally be in the ranges of:

	Medication	<1%-20%
	Solvent for medication	<1%-20%
25	Organogel	20%-40%
	Carrier/release agent	40%-70%

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It will of course be understood that these ranges represent the typical ranges for the specific example upon which the Figure is based, i.e., an example with a lecithin organogel, ketoprofen as the drug, and a "Pluronic NF-127" polyoxymer as the drug release agent. In general the ranges for other 5 compositions of this invention in which other suitable organogels, drugs, carriers and release agents are used will be similar, and those skilled in the art will have no difficulty formulating suitable compositions from the description herein.

Other factors will need to be considered in preparing specific formulations. If the carrier concentration in the cream lies above the useful range, it becomes 10 relatively stiff and difficult to apply, or, conversely, if the concentration falls below the suitable level, the cream will have a tendency to separate. Further, the pH of the cream must be adjusted to match the pH of the solubilized medication component to maximize the amount of non-ionized drug present in the cream. All suitable medications have acid/base characteristics that can be altered by 15 adjustment of the pH of the composition. The greater proportion of non-ionized drug present, the greater the drug's solubility and the greater the ability for larger quantities of the drug to be transported transdermally. The control of the pH can also be used to determine whether the drug is likely to become absorbed systemically or to be absorbed locally, since the speed of transdermal transport 20 will be dependent on the pH.

The physical properties of the cream will also be important. As noted the viscosity must be such that it can be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered transdermally to the patient. It must also be capable 25 of being removed from the patient's skin with ordinary physiologically acceptable cleansers or solvents, so that the cream may be removed if medically necessary,

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or the residue may be removed once the treatment time period for each administration has been completed. The components must be capable of being blended into a smooth, homogenous mixture with a cream- or lotion-like consistency and appearance, which either has a natural light colored  
5 appearance or can be lightly tinted if flesh-compatible tones are desired. The cream must also be capable of being covered with a light gauze or other type of dressing if desired, particularly where the cream would otherwise be in contact with the patient's clothing.

Adjustment of pH, effects of concentration and achievement of suitable  
10 physical properties in compositions containing polyoxymers have been studied and reported by Chi et al., *J. Pharm. Sci.*, **80** (3): 280-283 (1991). Reference is made to that article, and the prior references reported therein, for guidance in determining practical limits of pH, concentration, viscosity and the like when varying the specific materials herein. The techniques and methods reported  
15 there are quite suitable for use in the present invention.

Examples of the formation of different components are given below:

#### EXAMPLE 1

##### Formation of a Lecithin Organogel

A number of different lecithin organogels were formed by mixing different  
20 quantities of granular lecithin soya with isopropyl palmitate and a solvent . In three different typical compositions the respective amounts of lecithin soya and isopropyl palmitate were 25%/75%, 50%/50%, and 75%/25%. The first composition can be characterized as a thin oil, the second as a medium oil and the third as a heavy oil. In all cases the lecithin granules and isopropyl palmitate  
25 were allowed to sit for several hours, commonly overnight, by the end of which a liquid of oil or syrup consistency had formed. Alternatively one can mix the

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lecithin soya and the isopropyl palmitate at 50° to 60°C until the dissolution is complete.

At any point during formation of the mixture one can also add the drug or medication. If the latter is soluble in alcohol it may be previously dissolved in the  
5 alcohol and the alcohol/drug mixture incorporated into the lecithin soya and isopropyl palmitate mixture.

#### EXAMPLE 2

##### Formation of a Carrier/Drug Release Agent Component

A polymeric gel for use as a carrier was formed by mixing 20 grams of a  
10 commercial polyoxymer designated as "Pluronic NF-127" with 0.2 g of pure potassium sorbate and adding sufficient refrigerated purified water to bring to volume of 100 ml. Other similar compositions were formed with 30 g and 40 g of the "Pluronic NF-127" respectively. A typical commercial mixer was used to mix the material. Once all of the granules of the polymeric material had been  
15 wetted the gel was refrigerated so that dissolution took place upon cooling in the refrigerator. The compositions must be maintained under refrigeration because at ambient conditions they will solidify, since (as opposed to water) polyoxymer mixtures as prepared herein solidify when heated and liquefy when cooled.  
Stock solutions of these materials may be made and kept in refrigerated storage  
20 for repeated use in the formulation of the compositions of the present invention.

#### EXAMPLE 3

##### Mixture of a Cream-Containing Medication, Lecithin Organogel and Carrier/Drug Release Agent

In a typical procedure equivalent weights of the lecithin soya and the  
25 isopropyl palmitate are combined and a small quantity of sorbic acid is incorporated to control pH. The mixture is stirred until a syrup or oil consistency is obtained. Large quantities may be prepared and kept as a stock solution. The

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drug or medication, e.g., ketoprofen, is dissolved in water, alcohol or an equivalent solvent by using a the minimal amount of solvent necessary to obtain complete solubilizing. The dissolved drug is added to a small portion of the lecithin organogel and stirred to disperse the drug in the gel. The mixture of the  
5 carrier and the polyoxymer is then added to bring the entire formulation to the desired volume, and, if necessary, the pH of the cream is adjusted.

It will be evident that there are numerous embodiments of this invention which, while not expressly described above, are clearly within the scope and spirit of the invention. The above description is therefore intended to be  
10 exemplary only, and the scope of the invention is to be limited solely by the appended claims.

WE CLAIM:

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### CLAIMS

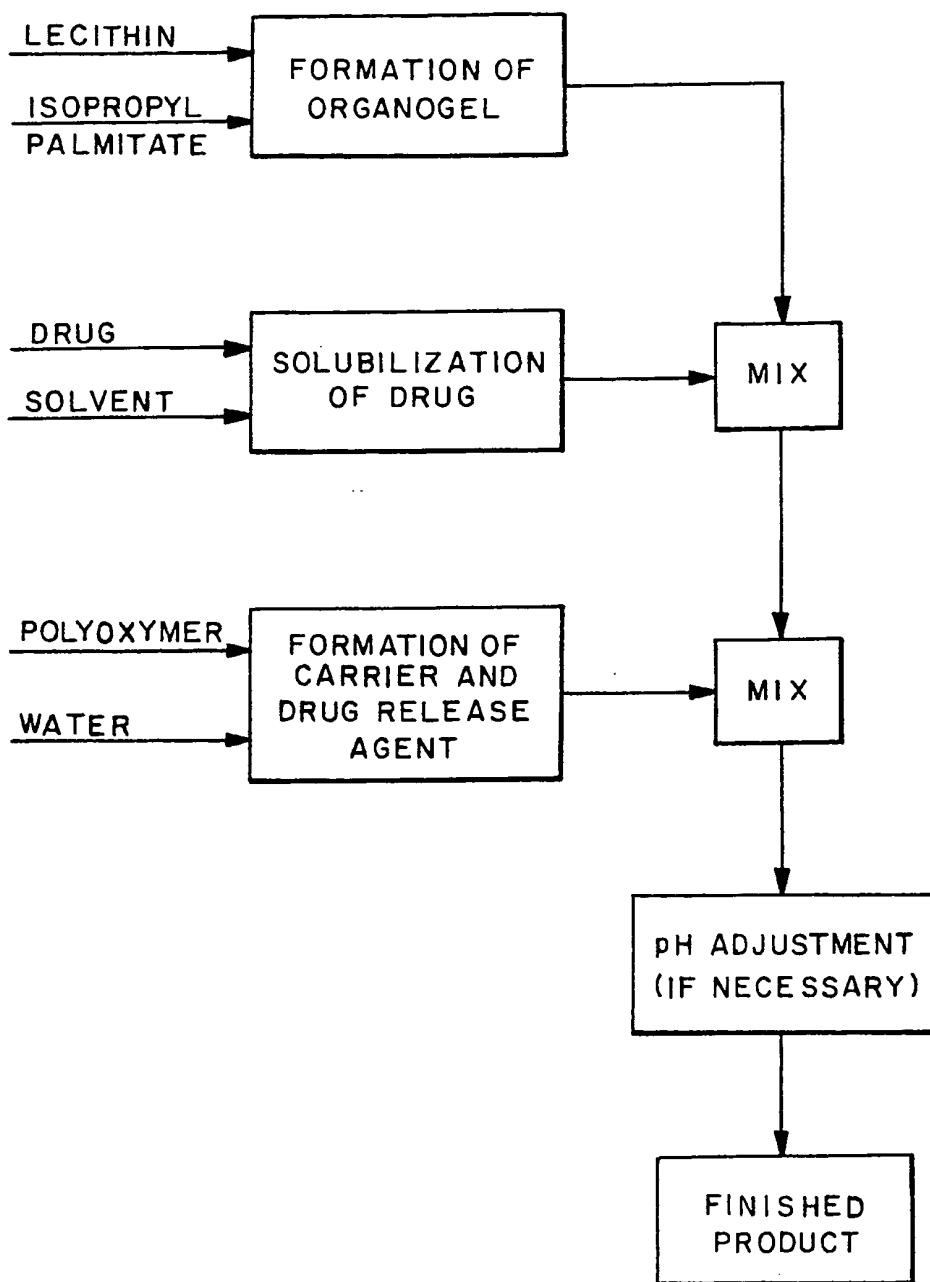
1. A composition useful for diffusional transdermal delivery of medication to a patient, characterized by inclusion of
  - a. a medication capable of being administered transdermally;
  - 5 b. a solvent for said medication;
  - c. a first penetration enhancer which improves diffusion of said medication into and within said patient's skin; and
  - d. a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration;
- 10 said composition having a viscosity in a range such that when applied topically, said composition conforms to and adheres to said patient's skin for a period of time sufficient for a significant portion of said medication to be delivered transdermally to said patient.
- 15 2. A composition as in Claim 1 wherein said medication is a lipophilic, hydrophilic or amphoteric therapeutic compound.
3. A composition as in Claim 1 or 2 wherein said first penetration enhancer is an organogel and has the property, when applied topically to a patient's skin, of enlarging openings in the stratum corneum, whereby said medication can diffuse through said enhanced openings at a rate greater than its diffusion rate through corresponding unenlarged openings.
- 20 4. A composition as in Claim 3 wherein said organogel is a fatty acid phospholipid emulsifying agent and a fatty acid or ester thereof.
- 25

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5. A composition as in Claim 1 wherein said second penetration enhancer alters the interaction between said medication and said composition to improve diffusion of said medication out of said composition for transdermal migration.
- 5 6. A composition as in Claim 5 wherein said second penetration enhancer is a polyoxymer.
7. A composition as in Claim 1 further characterized by including:
  - a. <1 to 20 parts by weight of said medication capable of being administered transdermally;
  - b. <1 to 20 parts by weight of said solvent for said medication;
  - c. 20 to 40 parts by weight of said first penetration enhancer which improves diffusion of said medication into and within said patient's skin; and
  - d. 40 to 70 parts by weight of said a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration.
8. A method for the preparation of a therapeutic composition to be transdermally administered, characterized by inclusion of the following steps:
  - 20 a. solubilizing a medication capable of being administered transdermally;
  - b. forming an organogel comprising a first penetration enhancer which improves diffusion of said medication into and within said patient's skin, and a solvent for said solubilized medication;
  - c. forming a polymeric component comprising a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration; and

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- d. blending said solubilized medication, organogel and polymeric component to form said composition having a viscosity in a range such that when applied topically, it will conform to and adhere to said patient's skin for a period of time sufficient for a significant portion of said medication to be delivered transdermally
- 5 to said patient.
9. A method as in Claim 8 wherein said medication is a lipophilic, hydrophilic or amphoteric therapeutic compound.
10. 10. A method as in Claim 8 further characterized by:
  - a. solubilizing <1 to 20 parts by weight of said medication capable of being administered transdermally;
  - b. forming 20 to 40 parts by weight of said organogel comprising a first penetration enhancer which improves diffusion of said medication into and within
  - 15 said patient's skin, and a solvent for said solubilized medication;
  - c. forming 40 to 70 parts by weight of said polymeric component comprising a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration; and
  - d. blending said solubilized medication, organogel and polymeric component
  - 20 to form said composition having a viscosity in a range such that when applied topically, it conforms to and adheres to said patient's skin for a period of time sufficient for a significant portion of said medication to be delivered transdermally to said patient.



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23014

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 A61K47/10 A61K47/24

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06636 A (CRANDALL, WILSON ) 7 March 1996 see claims 1,3 see page 6, line 23 - page 7, line 1 see page 8, line 6 - line 13 see example 1 ---	1-10
X	US 5 817 699 A (JOHN A. FLORES) 6 October 1998 see claim 1 see column 2, line 9 - line 26 ---	1-10
X	WO 95 11015 A (ELSON, MELVIN) 27 April 1995 see claims 8-12 ---	1-6,8,9 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance.
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 May 1999

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## INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 98/23014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 39746 A (ADVANCED POLYMER SYSTEMS) 30 October 1997 see claims 20-23 -----	1-6,8,9
E	WO 99 11208 A (WILLIAMS, C.) 11 March 1999 see claims 1-36 see examples 1-44 -----	1-10

**INTERNATIONAL SEARCH REPORT**

Information on patent family members			Int'l	Jonal Application No	
Patent document cited in search report	Publication date	Patent family member(s)		PCT/US 98/23014	
WO 9606636	A 07-03-1996	US 5560910 A AU 3417595 A CA 2198362 A EP 0777496 A		01-10-1996 22-03-1996 07-03-1996 11-06-1997	
US 5817699	A 06-10-1998	NONE			
WO 9511015	A 27-04-1995	US 5510391 A AU 684850 B AU 8089494 A CA 2174666 A EP 0727985 A JP 9502450 T		23-04-1996 08-01-1998 08-05-1995 27-04-1995 28-08-1996 11-03-1997	
WO 9739746	A 30-10-1997	AU 2804297 A		12-11-1997	
WO 9911208	A 11-03-1999	NONE			

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